CHAPTER 60

Blood Transfusion Therapy

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OBJECTIVES

This chapter will:

1. Review the transfusion indications for red blood cells, platelets, plasma, and cryoprecipitate in critically ill patients.
2. Outline the principles of massive transfusion.
3. Discuss common transfusion reactions and their management.

Over the last two decades, multiple randomized controlled trials (RCTs) have been conducted to evaluate clinical effects of transfusion in various patient populations. Information gleaned from these clinical trials formed current guidelines for administration of blood components. This chapter will provide a brief update on the evidence-based indications for blood product transfusions as well as its attendant risks.

BLOOD COMPONENTS

Whole blood usually is processed into blood components (red blood cells [RBCs], platelets, and plasma) so that each component can be stored at its optimal condition and patients receive only the specific blood components they need. Automatic cell separation (apheresis) technology can also be used to collect RBCs, platelets, and/or plasma. A single apheresis platelets (single-donor platelets) collection or 4 to 5 units of pooled platelets contain sufficient numbers of platelets for a therapeutic dose in an adult patient.

The shelf life of RBC component is determined by the anticoagulant and preservative used; the most commonly

used additive solution (ADSOL) allows for up to 42 days of storage at 4°C (1°–6°C) for RBCs. The volume is approximately 350 mL, of which 200 mL is red cells (hematocrit around 60%). In a 70-kg adult, transfusion of one unit RBCs is expected to increase the hemoglobin by 10 g/L or hematocrit by 3%. Platelets are stored at 20° to 24°C with constant agitation for maximum of 5 days. Four to five units of whole blood–derived platelets or one unit of apheresis platelets can increase platelet count by 20 to 40 × 10^9/L in a 70-kg patient. Fresh frozen plasma (FFP) is frozen and stored at –18°C within 8 hours of collection. It is thawed at 37°C and then stored at 4°C for 24 hours. FFP has a volume of 200 to 250 mL and contains "normal" level of all coagulation factors. Thawed plasma is similar to FFP but can be stored up to 5 days at 1° to 6°C and is clinically interchangeable with FFP. Cryoprecipitate is made from thawing FFP in cold temperature (between 1° and 6°C) and recovering the precipitate. Cryoprecipitate contains fibrinogen (≥150 mg), Factor VIII (≥80 IU), Factor XIII, Von Willebrand factor (vWF), and fibronectin in approximately 5 to 20 mL of plasma; therefore it is a more concentrated source of these coagulation factors than plasma.[1]

Leukocyte-Reduced Blood Components

White blood cells (WBCs) in the blood components can mediate adverse effects. White cells are removed primarily by filtration or apheresis processing. Leukocyte-reduction filters remove 3 to 5 logs (99.9% to 99.999%) of WBCs from whole blood–derived RBCs and platelet components. Leukoreduction can be performed before the component is stored (prestorage leukoreduction) or at the time blood is issued for transfusion (poststorage leukoreduction). Components collected by apheresis technology usually are leukoreduced as part of the collection. The benefits of leukocyte-reduced blood components include: prevention or decrease the incidence of HLA allo-immunization (and platelet refractoriness), reduction of the incidence of febrile nonhemolytic transfusion reactions, and reduction of transfusion-transmitted WBC-associated viruses such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV).[1] Other potential benefits, such as avoiding immunomodulatory effects of transfusion, remain controversial.

EVIDENCE-BASED BLOOD COMPONENT THERAPY

Red Blood Cell Transfusion

Anemia is prevalent in critically ill patients; consequently blood transfusion is a frequent intervention: more than one third of all ICU patients receive transfusion, 70% if the ICU stay is longer than 1 week.[2] Optional management of anemia in this population is a topic of much controversy and ongoing research. RBCs should be transfused with the goal of improving tissue oxygenation in the context of anemia or acute blood loss.

One of the best pieces of evidence for the hemoglobulin threshold for RBC transfusion in the critical care setting derived from the landmark Transfusion Requirements in Critical Care (TRICC) trial published in 1999[3] in which patients assigned to a restrictive transfusion strategy (hemoglobin < 70 g/L) had similar mortality rates compared with patients assigned to a liberal transfusion strategy (hemoglobin < 100 g/L). The mortality was lower in the restrictive strategy group in patients who were younger than 55 years old and less ill (Acute Physiology and Chronic Health Evaluation score < 20). The patients in the restrictive group also had lower multiple-organ dysfunction scores, myocardial infarction, and pulmonary edema.[3]

Many studies have been conducted subsequently to evaluate different hemoglobin thresholds among various patient populations.[4–8] The TRACS (Transfusion Requirements After Cardiac Surgery) trial compared a restrictive (hematocrit < 24%) to a liberal (hematocrit < 30%) transfusion strategy in cardiac surgery patients and showed no difference in the composite 30-day mortality and morbidity (cardiogenic shock, ARDS, and acute kidney injury) between the two groups.[4] In the FOCUS (Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair) study of 2016 patients with cardiovascular disease or risk factors after hip fracture surgery (mean age 82 years old), there was no difference in overall mortality and ability to walk independently at 60-day follow-up between a liberal transfusion strategy (hemoglobin threshold of 100 g/L) and a restrictive transfusion strategy (symptomatic anemia or hemoglobin threshold of 80 g/L).[5] In a study comparing restrictive (hemoglobin threshold < 70 g/L) and liberal (hemoglobin threshold < 90 g/L) strategy in patients with acute upper gastrointestinal bleeding, the survival rate at 6 weeks was higher in the restrictive-strategy group than in the liberal-strategy group (95% vs. 91%; hazard ratio for death with restrictive strategy, 0.55; 95% confidence interval [CI], 0.33 to 0.92; p = .02).[6] A study of 998 ICU patients with septic shock found no difference in mortality at 90 days and rates of ischemic events and use of life support in patients transfused using a restrictive strategy (hemoglobin < 70 g/L) versus a liberal strategy (hemoglobin < 90 g/L).[7] A more recent study of cardiac surgery patients found no significant differences in primary outcomes (serious infection or ischemic event) between the restrictive (hemoglobin level < 75 g/L) versus liberal (hemoglobin level < 90 g/L) transfusion groups.[8]

These RCTs support the safety of a restrictive transfusion policy. A meta-analysis of 31 RCTs of restrictive versus liberal red cell transfusion strategies involving nearly 10,000 patient found no difference in mortality, overall morbidity, acute myocardial infarction, or renal failure.[9] Another meta-analysis of the restrictive verse liberal transfusion strategies in patients with cardiovascular diseases in a noncardiac surgery setting studied 11 RCTs involving 3033 patients.[10] The pooled risk ratio for the association between transfusion thresholds and 30-day mortality was 1.15 (95% CI: 0.88 to 1.50, p = .50) with little heterogeneity (I^2 = 14%). The risk for acute coronary syndrome was increased in patients managed with restrictive (nine trials, risk ratio 1.78, 95% CI: 1.18 to 2.70, p = .01, I^2 = 0) compared with liberal transfusion.[10] The authors suggest the use of a more liberal transfusion threshold (>80 g/L) for patients with acute and chronic cardiovascular disease until adequately powered high-quality RCTs are conducted in this patient population.[10] An analysis[11] evaluated the outcomes associated with transfusion in ICU patients with severe acute kidney injury requiring continuous renal replacement therapy by comparing 977 patients who received at least one red cell transfusion with 488 untransfused patients enrolled in the Randomized Evaluation of Normal Versus Augmented Level (RENAL) replacement therapy study,[12] a study that found no difference in its primary outcome of 90-day mortality in those threatened with high or low continuous renal replacement therapy (CRRT).[12] This secondary analysis found no association of RBC transfusion with 90-day mortality

BOX 60.1

Guidelines for Red Blood Cell Transfusion in Critically Ill Patients

1. Transfusion should be given only when expected benefits outweigh the risks.
2. Hemoglobin ≤70 g/L and/or hematocrit ≤22% in a hemodynamically stable patient in the ICU (acute coronary syndromes excluded).
3. Transfusion may be appropriate when hemoglobin ≤80 g/L and/or hematocrit ≤24% in patients with cardiac, cerebral, or other major organ disease.
4. Transfusion may be appropriate when hemoglobin ≤ 100 g/L or hematocrit ≤ 30% associated with acute ischemic cardiovascular disease (angina pectoris, myocardial infarction).

BOX 60.2

Guidelines for Platelet Transfusion in Critically Ill Patients

1. Platelet count less than 50×10^9/L before an invasive procedure or in a patient with active bleeding
2. Platelet count less than 10×10^9/L in a stable patient
3. Platelet dysfunction documented by abnormal platelet function tests (closure time, TEG) in a bleeding patient

TEG, Thromboelastography.

or other patient-centered outcomes.[11] Although this study did not address the optimal hemoglobin threshold in this specific patient population, accumulating evidence from RCTs in ICU patients,[3,9] including patients with septic shock,[7] suggests that a restrictive transfusion strategy is likely to be safe in this patient population.

In clinical practice guidelines for RBC transfusion from the AABB Advancing Transfusion and Cellular Therapies Worldwide (formerly, the American Association of Blood Banks), four conclusions were made based on the quality of evidence from clinical trial data (Box 60.1)[13]:

1. Strong recommendations for adhering to a restrictive transfusion strategy (70 to 80 g/L) in hospitalized, stable patients (high-quality evidence)
2. Suggestion for (weak recommendation) adhering to a restrictive strategy in hospitalized patients with preexisting cardiovascular disease and considering transfusion for symptoms or a hemoglobin of 80 g/L or less (moderate-quality evidence)
3. No recommendations for or against a liberal or restrictive transfusion threshold for patients with acute coronary syndrome (very low-quality evidence)
4. Suggestion for (weak recommendation) that transfusion decisions be influenced by symptoms as well as hemoglobin level (low-quality evidence)[13]

The National Clinical Guideline Center (NCGC) (UK) published recommendations (2015)[14] that suggest a hemoglobin level of 80 to 100 g/L be used for patients with acute coronary syndrome, but further studies are needed to determine the optimal transfusion threshold for patients with chronic cardiovascular disease (Box 60.1).[10,14]

Red Blood Cell Storage Lesion

Stored RBCs undergo metabolic and structural changes including decrease in intracellular adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (2,3-DPG), increase in extracellular concentration of potassium, and changes in morphology. In the United States, the mean storage period for RBCs transfused to ICU patients ranged from 16 to 21 days.[2] Recently, concerns over the age of transfused RBCs have been raised as a contributing factor to morbidity and mortality.[15] A review of more than 20 studies in adult patients concluded that it is difficult to assign a causal relationship between the age of transfused RBC and adverse clinical outcomes.[16] Two large multicenter randomized clinical trials, including the ABLE[17] (Age of Blood Evaluation) study in ICU patients in Canada and the RECESS[18] (Red Cell Storage Duration) study of cardiac surgery patients in the United States, recently have been reported. Both studies failed to show a difference in patient outcomes between those transfused with fresher units versus those transfused with older units. These studies suggest that, although red cells show in vitro changes with storage, these changes are not associated with adverse clinical effects.[17,18]

Platelet Transfusion

Platelets are used to treat (therapeutic) or prevent (prophylaxis) bleeding because of deficiencies in platelet number or function. In patients with active bleeding or planned surgical procedures, platelet transfusions are indicated for platelet counts of below 50×10^9/L (Box 60.2).[1,19] Higher counts may be needed for bleeding at critical anatomic locations, such as neurologic or ophthalmologic surgery. In nonbleeding stable patients with hypoproliferative thrombocytopenia, prophylactic transfusion for a platelet count of below 10×10^9/L is indicated to prevent spontaneous bleeding.[1,19] In patients with high risk for spontaneous bleeding resulting from risk factors such as high fever, sepsis, disseminated intravascular coagulation (DIC), or splenomegaly, prophylactic transfusions for platelet count of below 20×10^9/L are a reasonable approach.

The expected response to a platelet transfusion is an increment of 20 to 40×10^9/L in a 70-kg adult at 1 to 4 hours after the transfusion.[1] Patients with poor responses should be evaluated for immune refractoriness resulting from HLA-antibodies. HLA-matched or crossmatch-compatible platelets can achieve successful responses in the majority of patients who are HLA alloimmunized. Leukoreduction can be used to prevent platelet refractoriness resulting from HLA alloimmunization.[1,19]

Plasma and Cryoprecipitate Transfusion

Plasma transfusions are indicated for patients who are bleeding or undergoing invasive procedure with multiple coagulation factors deficiencies (Box 60.3).[1,14] Each unit of plasma is 200 to 250 mL, and the recommended dose is 15 to 20 mL/kg. Plasma transfusion for an invasive procedure has not been shown to be of benefit in patients with INR < 2.0 and would probably have minimal or no effect on the INR.[20]

Cryoprecipitate is used to control bleeding or before invasive procedures in patients with fibrinogen deficiency (fibrinogen level less than 1.0 g/L).[1,14]

Urgent and Massive Transfusion

Urgent transfusion refers to the administration of blood products before the pretransfusion compatibility testing is

BOX 60.3

Guidelines for Transfusion of Plasma and Cryoprecipitate in Critically Ill Patients

1. Plasma is indicated in the treatment of thrombotic thrombocytopenic purpura (TTP).
2. Plasma transfusion may be appropriate to correct warfarin effects in cases of active bleeding or emergency surgery when prothrombin complex concentrate (PCC) is not available.
3. Plasma transfusion may be indicated before an invasive procedure or in a patient with active bleeding resulting from multiple coagulation factor deficiency (INR > 1.5).
4. Plasma may be transfused in patients with coagulation disorder undergoing surgery or invasive procedure where INR elevation is due to nonwarfarin mechanism (INR > 1.5).
5. Cryoprecipitate may be indicated in active bleeding or before invasive procedure in patients with hypofibrinogenemia (fibrinogen level less than 1.0 g/L).
6. Cryoprecipitate may be used to treat von Willebrand (VW) disease when VW factor containing concentrates is not available.
7. Cryoprecipitate may be used to control uremic bleeding after other modalities have failed.

completed. In patients with an unknown blood type, group O RBCs and group AB plasma products should be used. Rh-negative RBCs should be used for children and females with childbearing potential to avoid the possible sensitization to the D antigen.

Massive transfusion refers to the replacement of one or more blood volumes within 24 hours. Transfusion of large amounts of cold, citrated blood products can lead to hypothermia, dilutional coagulopathy, and acid-base imbalance. Blood warmers may be used. The use of all blood components should be guided ideally by laboratory results. However, in trauma and massive transfusion setting, it may be necessary to empirically transfuse before laboratory results are available. Many hospitals have trauma transfusion protocols in which a predetermined plasma : platelets : RBC ratio is transfused. The recently published Pragmatic Randomized Optimal Platelet and Plasma Ratio (PROPPR) trial compared the transfusion of plasma, platelets, and RBCs in a 1:1:1 ratio versus 1:1:2 ratio and mortality in patients with severe trauma and major bleeding, and found no significant differences in mortality at 24 hours (12.7% in 1:1:1 group vs. 17.0% in 1:1:2 group; difference, –4.2% [95% CI, –9.6% to 1.1%]; $p = .12$) or at 30 days (22.4% vs. 26.1%, respectively; difference, –3.7% [95% CI, –10.2% to 2.7%]; $p = .26$).[21] The 1:1:1 ratio group had less bleeding and higher survival at 3 hours with no increase in complications.[21] This has led some to recommend the early use of a balanced 1:1:1 blood product ratio in massive bleeding trauma patients.[22] Platelet counts should be maintained above 50×10^9/L, and cryoprecipitate should be given to maintain the fibrinogen level above 1.0 g/L. Whole blood clotting assays, such as thromboelastography (TEG) and rotational TEG (RoTEG) should be used to guide transfusion therapy in trauma and massive transfusion settings.[23]

Adverse Effects of Blood Transfusion

Major improvements have been made in blood safety over the last 20 years, particularly with the implementation of direct viral detection methods using nucleic acid testing. The risk of HIV and HCV transmission through blood transfusion is less than 1 in a million (Table 60.1).[13,24,25] Although the risk of known viruses has become minimal, noninfectious risks are now the most common causes of transfusion-related morbidity and mortality, including transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), and acute hemolytic reactions.

TABLE 60.1

Risks of Transfusion-Transmitted Viral Infections Data[13,24,25]

VIRUSES	ESTIMATED RISK IN UNITED STATES
Human immunodeficiency virus (HIV)	1:1,467,000
Hepatitis C virus (HCV)	1:1,149,000
Hepatitis B virus (HBV)	1:843,000 to 1:1,208,000

Modified from Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: a clinical practice guideline from the AABB*. *Ann Intern Med.* 2012;157:49–58; Zou S, Dorsey KA, Notari EP, et al. Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing. *Transfusion.* 2010;50:1495–1504; Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. *Blood.* 2009;113:3406–3417.

Acute hemolytic transfusion reactions are caused by immune-mediated lysis of transfusion red cells via complement activation (intravascular hemolysis). Symptoms/signs include fever, chills, hemoglobinemia, hemoglobinuria, shock, and DIC. The most common cause is infusion of ABO-incompatible blood because of human clerical error. Treatments include hydration, diuretics, blood pressure support, and treatment of DIC if present. Careful patient identification at the time of pretransfusion specimen collection and blood administration are keys in preventing acute hemolysis caused by ABO-incompatible transfusions.[1] With approximately 13.5 million RBC transfused each year in the United States, the estimated risk of death resulting from hemolysis is 1 in 1,250,000 (or 8 per 10 million RBC units).[13]

Febrile nonhemolytic transfusion reactions (FNHTR) are characterized by fever (≥1°C elevation) that may be accompanied by chills, rigors, hypertension, tachycardia, and dyspnea without another clinical explanation. Leukocytes and cytokines released by leukocytes in the blood components are the primary cause of FNHTR; therefore the reaction occurs more frequently in patients receiving non–leukocyte-reduced components. Leukoreduction (especially when performed before storage) has been shown to reduce the incidence of FNHTR to RBC and platelet transfusion.[1] FNHTR may occur in less than 1% of transfusions with RBCs (between 0.04 and 0.44 per 100 units). The incidence of FNHTR with platelets has been reported to be between 0.06 and 2.2 reactions per 100 transfusions.[1]

Allergic reactions to plasma proteins are characterized by histamine-mediated urticarial rash occurring in 1% to 3% of transfused patients.[1] In mild localized allergic reactions, transfusion can be temporarily stopped and the patient treated with antihistamines. If symptoms resolve, the transfusion can be restarted slowly with close observation. Future similar reactions can be prevented with pretransfusion medications using antihistamines and if the reaction was more severe, steroids 30 to 60 minutes before the start of the transfusion. Anaphylactic reactions to blood products are rare, occurring in patients with antibodies against plasma proteins such as IgA or haptoglobin. Patients with severe

allergic or anaphylactic reactions should be treated with fluid resuscitation, epinephrine, and steroids. Washed cellular blood components (RBCs and platelets) are indicated.[1] Patients with anaphylactic reactions resulting from IgA deficiency should receive IgA deficiency plasma, which can be obtained through rare-donor registry.[1]

TRALI is manifested as acute onset of dyspnea, hypoxia, and noncarcinogenic bilateral pulmonary edema within 6 hours of blood product transfusion without another cause. It is an inflammatory process caused by various stimuli in the blood product, usually antibodies to white cells or neutrophils or proinflammatory molecules, which in turn leads to activation of neutrophils and complement in the pulmonary vasculature resulting in capillary leakage syndrome.[1] Treatment is supportive with oxygen and mechanical ventilation. With the recognition of the roles of donor HLA antibodies in the pathogenesis of TRALI, blood centers have implemented strategies to reduce TRALI risk using plasma from low-risk donors. As a result, the incidence of TRALI and associated mortality has declined significantly.[1] The rate of TRALI in 2009 was 0.81 (95% CI: 0.44 to 1.49) per 10,000 transfused blood components according a large prospective study.[26]

TACO is cardiogenic pulmonary edema resulting from the rapid and/or excessive transfusion of blood products to a patient with limited/compromised cardiac reserve or renal disease. Even small transfusion volume can precipitate symptoms in at-risk patients with positive fluid balance. Treatments include diuresis and supportive cardiopulmonary care.[1] The estimated incidence of TACO is 1% to 4%.[13]

Bacterial contamination of blood components is a rare but serious complication. Patients may experience high fever, chills/rigors, and even shock. Aggressive therapy and broad-spectrum antibiotics should be started if a septic reaction is suspected. Blood cultures also should be drawn from the patient. The implicated component should be sent for culture.[1]

Alternative to Blood Transfusion

Several strategies can be used to reduce allogeneic blood product transfusions. Blood salvage during surgery and immediate postoperative period is gaining traction as a strategy for reducing blood transfusion. Strategies for reducing iatrogenic blood loss include the use of small-volume phlebotomy tube, elimination of redundant and unnecessary laboratory testing, and the use of point-of-care testing and noninvasive testing. Antifibrinolytic agents such as tranexamic acid and epsilon-aminocaproic acid have been used to decrease blood loss in cardiac surgery setting, control bleeding in patients on extracorporeal membrane oxygenation (ECMO), and in the management of thrombocytopenic bleeding. The available data on erythropoietin (EPO) indicates that it does not improve survival in critically ill patients. There may be increased risk for thrombotic complications.[20] There are no safe and effective hemoglobin-based oxygen carriers to replace blood.

CONCLUSION

Several RCTs indicate that restrictive RBC transfusion practice using a hemoglobin of less than 70 g/L is safe in critically ill patients. Although similar RCTs are not available for plasma or platelet transfusion guidelines, a large body of observational studies suggests that plasma transfusion for an invasive procedure has not been shown to benefit patients with INR less than 2.0. Similarly, in thrombocytopenic patients, the target platelet count for bleeding or for an invasive procedure is 50×10^9/L.

Viral transmission risk has become exceedingly low. Other risks, such as TACO and to a lesser extent TRALI, are much more common. Storage of red cells does not seem to be associated with adverse clinical outcomes. Alternatives to transfusion using hemostatic agents, salvaged blood, and adherence to evidence-based transfusion guidelines are likely to reduce the need for transfusion in critically ill patients.

Key Points

1. Avoid unnecessary transfusion through adhering to the evidence-based transfusion guidelines. A restrictive RBC transfusion strategy (hemoglobin < 70 g/L) is recommended for hemodynamically stable patients in the critical care setting.
2. Optimal hemoglobin threshold for patients with unstable angina and acute coronary syndrome has yet to be determined.
3. Plasma transfusion for an invasive procedure has not been shown to be of benefit in patients with INR < 2.0.
4. The target platelet count for a bleeding patient or for an invasive procedure is 50×10^9/L.
5. The risk of transfusion transmitted human immunodeficiency virus (HIV) and hepatitis C virus (HCV) or hepatitis B virus infections is less than 1 in a million; other risks such as transfusion-associated circulatory overload (TACO) or transfusion-related acute lung injury (TRALI) are much more common.

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